International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
www.pharmacysciencejournal.com
Volume 1; Issue 1; March 2016; Page No. 47-53

Preparation and evaluation of sustained release film: Coated tablets of nitrofurantoin

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Abstract
Sustained release drug delivery system offer advantages of attenuation of adverse effects, fewer fluctuations in plasma drug concentration, improved patient compliance, reduction in dosing frequency, etc. The present study attempt has been made to develop and evaluate sustained release film-coated tablets of nitrofurantoin. The designing of sustained release tablets was done using wet granulation technique and the polymers were used in varying proportions. The tablets were prepared using polymers such as HPMC K100M, HPMC E15 and different excipients. The prepared tablets were evaluated for hardness, friability, thickness, weight variation, drug content and in vitro dissolution studies. The mean values of the results of various evaluation parameters were statistically presented by plotting graphs. The in vitro release data were fitted into zero-order, first order, Higuchi and Korsemeyer-Peppas models. All formulated tablets showed acceptable pharmacotechnical properties and complies with pharmacopoeial specifications but batch F6 shows better results and release than other formulated tablets. The in-vitro release data was plotted for formulation F6 which indicates that drug release was governed by nearly zero-order kinetics. Formulation F6 showed no change in physical appearance, drug content after storage 40 ^{0}C±2 ^{0}C / 75% RH ± 5% for 3 months. Further, in-vivo and continuation of stability studies are recommended.

Keywords: Nitrofurantoin; Sustained release; HPMC K100M; Matrix tablets; HPMC E15; Zero order release

Introduction
The oral route is considered to be the most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorption from these regions of gastro-intestinal tract (GIT) depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the urinary tract is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the urinary tract or colon rather than upper GIT prefers number of advantages. A traditional oral sustained release formulation releases most of the drug, after the dosage form pass from the stomach. Hence, the drug should have absorption window either in the duodenum or intestine or urinary tract [1].

The main goal of sustained drug delivery systems is to improve the effectiveness of drug therapies [2]. Sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Ideally a sustained release oral dosage form is designed to release rapidly some pre-determined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate.

Nitrofurantoin is a urinary tract antibiotic [3]. The short biological half-life (0.3 to 1 hour) and dosing frequency more than one per day make Nitrofurantoin an ideal candidate for sustained release [4]. To reduce the frequency of administration from four times daily to two times daily, to minimize the side effects of nausea and emesis and to improve patient compliance, a sustained release tablet formulation of nitrofurantoin is desirable. The present study aims to develop sustained release matrix tablets using hydrophilic matrix materials, such as HPMC E15, HPMC K4M and HPMC K100M CR along with drug in varying proportions by wet granulation method.

Currently available sustained matrix tablets are generally prepared by wet granulation method. The aim of the present work was to prepare sustained release matrix tablets of nitrofurantoin and to study the effect of in-vitro release characteristics, kinetics of the prepared formulations and stability studies.

Materials and methods
Materials
Nitrofurantoin was procured from Panchsheel Organics Ltd., Indore, India. HPMC E15, HPMC K4M and HPMC K100M CR were obtained from Colorcon Asia Pvt. Ltd. Goa. Isopropyl alcohol (IPA) and Methylene dichloride (MDC) were obtained from Merck industries, Mumbai. Lactose monohydrate, Talc and Magnesium stearate were obtained from Qualigens Pvt. Ltd., Vijay Minerals and Amishi Drugs respectively. All other ingredients used were of analytical grade.

Methods
Formulation of sustained release tablets of nitrofurantoin
All ingredients, as mentioned in Table 1, were weighed accurately. Nitrofurantoin API and the intra-granular materials were co-sifted through 40# sieve and mixed properly. Granulation was done in rapid mixer granulator (RMG) first through water and kneading was done for 15-20

minutes. Because of less granulation, mixture of IPA and MDC in the ratio of 1:1 was added to obtain optimum granulation. Wet material was dried for 45 minutes in fluidized bed drier (FBD) at 50^0-55 ^{0}C till the desired (not more than 1.50% w/w at 105 ^{0}C by halogen moisture balance) loss on drying (LOD) is achieved. The dried granules were sized through 40# sieve.

Extra-granulation: The above granules were geometrically mixed with extra-granular excipients of respective batches and the blend was mixed well. The lubricated granules were then compressed.

Film-coating solution preparation and final coating of different batches Instacoat yellow ICR - 0307 (50 gm) was dispersed in 350 ml purified water under stirring in beaker. The dispersion was passed through muslin cloth. Finally the volume of the coating solution was made up to 500 ml. The coating of the tablets was done in Gans-coater. The target weight gain was 3% w/w over average weight. After achieving the target weight gain, the coated tablets were dried (cured) at 35 ^{0}C to 40 ^{0}C (bed temperature) for 30 minutes.

Table 1: Formula of different batches of SR tablets of nitrofurantoin

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Nitrofurantoin*	100	100	100	100	100	100	100	100	100
Lactose IP*	99	99	99	99	99	110	110	110	99
PVP K-30*	06	06	06	06	06	06	06	06	06
HPMC K4M	07***	13***	10***	07***	10***	12.5*	14*	14*	16*
HPMC E15	28***	22***	20***	18***	16***	10**	10**	8.5**	10**
HPMC K100M CR	X	X	05***	06***	05***	X	X	X	05*
Super tab 11SD***	X	X	X	04	2.5	X	X	X	04
Magnesium stearate***	1.5	1.5	1.5	1.5	03	03	1.5	03	1.5
Talc***	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight of uncoated tablet	245	245	245	245	245	245	245	245	245
Instacoat Aqua - III yellow	05	05	05	05	05	05	05	05	05
Total weight of coated tablet	250	250	250	250	250	250	250	250	250

*Intra-granular part **HPMC E15 incorporated along with binding solvent IPA: MDC. ***Extra-granular part

Preformulation studies of nitrofurantoin API

Determination of wavelength maxima by UV-Spectrophotometer - 1 ml standard stock solution (25 mg of nitrofurantoin in 10 ml of dimethylformamide) of nitrofurantoin was transferred into a 10 ml volumetric flask and volume was adjusted upto 10 ml with pH 7.5 phosphate buffer. The absorbance of the solution was scanned in the range of 200 to 400 nm in UV-visible spectrophotometer, Shimadzu - 1800, in medium scanning speed against pH 7.5 Phosphate buffer as a blank. Standard curve preparation of nitrofurantoin by UV- Spectrophotometer - A series of drug solutions ranging from, 10 µg/ml - 70 µg/ml were prepared from standard stock solution. A calibration curve for nitrofurantoin was obtained by measuring the absorbance of all the solutions at the lambda maximum of 367 nm against the blank. The standard curve was constructed for nitrofurantoin by plotting concentration versus absorbance. Identification by Infrared Spectroscopy - 2 mg of drug sample was taken with dry IR-grade potassium bromide (KBr) at about 2 % sample to KBr ratio in an agate mortar. KBr pellet of the drug sample was prepared. Normally background was first scanned by using blank potassium bromide pellet. Then the sample was scanned. The spectra were collected in the 400 cm^{-1} to 4000 cm^{-1} region with 8 cm^{-1} resolution, 60 scans and beam spot size of 10-1000 µm. Differential Scanning Calorimetric (DSC) Procedure - Differential Scanning Calorimetry (DSC) was performed using DSC-60, Shimadzu calorimeter. Around 1-1.5 mg of API was weighed in a sample pan and subjected to program heating under nitrogen atmosphere on an aluminium pan at a heating rate of 10^0C/min over the temperature range of 5 ^{0}C and 300 ^{0}C. DSC analysis was carried out under nitrogen gas flow of 20 $lb/inche^2$. Identification by Nuclear Magnetic Resonance (NMR) Spectrum - Proton NMR spectra was recorded on a Varian 400 spectrometer. Proton chemical shifts are reported in ppm relative to internal tetramethylsilane (TMS, 0.0 ppm). The NMR spectrum for nitrofurantoin (Norwich Pharmacal Reference Standard Purity) was prepared in DMSO - d_6, containing a tetramethylsilane as the internal reference.

Pre-compression parameters (Evaluation of granules)

Bulk density (BD) - Weigh accurately 25 gm of powdered blend, which was previously passed through 30 # sieve, and transferred in 100 ml graduated cylinder. The blend was carefully leveled without compacting, and the unsettled apparent volume (V_0) was read. The test was done in triplicate. Calculate the apparent bulk density in g/ml by the following formula –

$$\textbf{Bulk Density} = \textbf{Weight of powder/Bulk Volume}$$

Tapped density (TD) – Weigh accurately 25 gm of granules, which were previously passed through 30 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanical tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 250 drops per minute. Tap the cylinder for 500 times and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping for an additional 750 times and measure the tapped volume (V_2) to the nearest graduated

units. If the difference between the two volumes is less than 2%, then the final tapped volume (V_2) is taken into consideration. The readings were taken in triplicate [5, 6]. Calculate the tapped density in g/ml by the following formula-

$$\textbf{Tapped Densit} = \textbf{Weight of powder/ Tapped Volume}$$

Carr's Index (% Compressibility) - The % compressibility of the powdered blend was determined by Carr's Index [7, 8, 9]. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is –

$$\textbf{Carr's Index} = \frac{\textbf{Tapped density-Bulk density}}{\textbf{Tapped density}} \times \mathbf{100}$$

Hausner's Ratio - The Hausner's Ratio is a number that is correlated to the flowability of a powder or granular material [8, 9].

$$\textbf{Hausner's Ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

Angle of repose - The angle of repose of powdered blend was determined using Enar reposogram, based on funnel method, in triplicate. The accurately weighed powder was taken in a funnel. The height of the funnel (constant) was adjusted in such a way that the tip of the funnel just touches the apex of the powder. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation

$$\tan \emptyset = \frac{\mathbf{h}}{\mathbf{r}}$$

Where Ø is angle of repose, h is the height of the pile of powder from base and r is the radius of the pile of powder from base [9]. Drug - excipients compatibility study - The primary objective of this investigation was to identify a stable storage condition for nitrofurantoin in solid state and identification of compatible excipients for its formulation [10]. In this method, different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. Seven sets of each mixture were prepared, for physical compatibility studies (visual observation only) for a period of one month, which were kept under different conditions.

Post compression parameters (Evaluation of nitrofurantoin SR tablets)

Description - The general appearance and elegance of tablet was identified visually, that includes tablet size, shape, color, presence or absence of an odor, taste, surface texture, absence of sticking, etc. Thickness and diameter - The dimensional specifications were measured using digital micrometer calipers. Twenty tablets were selected at random. The thickness of the tablet is mostly related to the tablet hardness and it can be used as initial control parameter. Hardness - The hardness of the twenty tablets from each formulation was determined using Inweka hardness tester. Weight variation - Twenty tablets from each formulation were selected at random and average weight was determined, then individual tablets were weighed and individual weight was compared with average weight. Friability - Weighed amount of twenty de-dusted tablets was placed in drum of friability test apparatus, i.e. Roche Friabilator. The apparatus was operated for 4 minutes at a speed of 25 rpm and tablets were then dusted and reweighed. Friability was calculated by the following formula –

$$\%\ \textbf{Friability} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Initial weight}} \times \mathbf{100}$$

A maximum mean weight loss from three samples of not more than 1 % is considered acceptable [11]. Assay - This test was performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 250 mg of Nitrofurantoin was dissolved in phosphate buffer pH 7.2 in 100 ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 265.5 nm using phosphate buffer pH 7.2 as blank and the % drug content was estimated [12]. Dissolution study - The study was carried out in 900 ml of phosphate buffer pH 7.2 at 75 rpm, which was maintained at 37 ^{0}C±0.5 ^{0}C using the USP apparatus type II (Electrolab Disso 8000). 5 ml samples were withdrawn at regular intervals of 1 hr and the absorbance was measured at 265.5 nm using Shimadzu UV spectrophotometer 1700. Sink condition was maintained by replacing with fresh buffer medium. The dissolution study was carried out for 10 hrs followed by mathematical treatment of the solved dissolution data [13]. Analysis of release data - The in-vitro release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsemeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [14, 15]. Stability study - Accelerated stability testing was carried out as per ICH guidelines. The trial batch F6, film coated, was placed in the stability at 40 ^{0}C±2 ^{0}C/75%±5% RH for 3 months. The tablets were packed in PVC Blister pack. Samples were collected after 1 month and finally after 3 months and dissolution was carried out in USP - II paddle apparatus, in pH 7.2 phosphate buffer at 75 rpm.

3. Results and discussion

Results of preformulation studies: The absorbance of the solution was scanned in the range of 200 to 400 nm and the lambda maximum was found to be 367 nm, which was taken as analytical wavelength. The calibration curve of nitrofurantoin was plotted against absorbance and concentration in pH 7.5 Phosphate buffer, as shown in Fig. 1. The curve was found to be linear in the range of 10 µg/ml to 70 µg/ml, with a slope of 0.009, intercept of 0.016 and R^2 value of 0.999. The IR of nitrofurantoin as KBr pellets was performed and its spectrum is shown in Fig. 2. The spectrum contains all the original peaks of the nitrofurantoin when compared with the innovator's sample, no chemical shift was found and hence the test sample was confirmed to be nitrofurantoin and safe to be used in the formulation.

Melting point of nitrofurantoin was determined by DSC technique. Nitrofurantoin showed sharp endothermic peak at 272 ^{0}C, corresponding to its melting point, indicating its crystalline nature, as depicted in Fig. 3. The NMR spectrum of nitrofurantoin in DMSO - d_6 containing a tetramethylsilane as the internal reference is shown in Fig. 4.

Results of pre-compression and post-compression parameters

Nine formulations of nitrofurantoin were prepared with different concentrations of HPMC K100 M, HPMC E15 and different excipients by using wet granulation method. For each formulation, blend of drug and excipients was prepared and evaluated for various parameters/properties. Bulk density was found in the range of 0.6231-0.6767 g/ml and the tapped density between 0.7160-0.7965 g/ml **(**Table 2). Using these two density data Hausner's ratio and compressibility index were calculated. The powder blend of all the formulations had Hausner's ratio of less than 1.25, indicating good flowability. The compressibility index was found between 12.90 and 15.04% and the compressibility-flowability correlation data indicates a fairly good flowability of the blend. The good flowability of blend was also evidenced angle of repose (value range of 28.16^0 - 31.35^0), which is below 40^0 indicating good flowability. Drug-excipient interaction was determined by using physical compatibility study by visual observation. No change in the initial color of the blend of nitrofurantoin with different excipients was observed after one month, at different temperature and humidity conditions. Hence the drug was found to be physically compatible with the different excipients used in the formulation. The prepared film coated matrix tablets were found to be yellow colored with round shape and evaluated for parameters such as thickness, hardness, friability, weight variation, assay, and in-vitro release. The film-coating of the sustained release tablets rendered them resistant to atmospheric effects such as air, moisture, etc. as well as made the tablets look elegant for patient's acceptance. Results for these parameters are shown in Table 3. Thickness of the tablets was measured by digital vernier calipers by picking tablets randomly from all the batches. The mean thickness was (n=20) almost uniform in all the formulations and value ranged from 3.45±0.3 mm to 3.65±0.3 mm for uncoated tablets and 3.55±0.3 mm to 3.75±0.3 mm for film coated tablets. The standard deviation values indicated that all formulations were within the range. Friability of the tablets was found below 1% indicating a good mechanical resistance of tablets. Since the powder material was free flowing, tablets thus obtained were of uniform weight due to uniform die fill, with acceptable weight variations as per pharmaceutical specifications. The assay result failed for F1 to F3 formulations, which may be due to improper mixing of drug with the excipients. The assay from F4 to F9 formulations was found in the range of 97.2 - 101.4% (acceptable limit) and the hardness of the film coated tablets between 4.5–7.0 kg/cm^2 (Table 3).

Results of in- vitro release profile indicated that among all the formulations, F6 was the most promising formulations as it showed 15%, 33.8% and 101.8% drug release within 1, 3 and 10 hrs., respectively as shown in Table 4 and all the physical parameters were compiled with pharmacopoeial specifications. The in-vitro release data was plotted for various kinetic models as shown in Fig. 5, 6, 7 and 8. The R^2 value for zero-order was found to be 0.998 which indicates that optimized formulation F6 was found to be nearly zero order drug release, governed by dissolution through matrix.

The optimized formulation (F6) was found to be stable under the test storage conditions of 40 ^{0}C±2 ^{0}C/75%±5% RH as there was no change in tablet properties in between and after completion of three - months stability study.

Table 2: Micromeritic properties of powder blends of different batches (n=3)

Powder blend	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	30.11 ± 1.576	0.6231 ± 0.028	0.7224 ± 0.039	13.98 ± 1.213	1.15 ± 0.031
F2	30.56 ± 1.328	0.6346 ± 0.025	0.7378 ± 0.016	13.74 ± 2.328	1.16 ± 0.032
F3	30.35 ± 0.914	0.6767 ± 0.029	0.7965 ± 0.026	15.04 ± 1.259	1.17 ± 0.039
F4	28.46 ± 1.004	0.6331 ± 0.023	0.7194 ± 0.023	13.69 ± 1.906	1.15 ± 0.028
F5	28.68 ± 0.876	0.6432 ± 0.055	0.7421 ± 0.045	13.32 ± 1.213	1.15 ± 0.013
F6	28.16 ± 1.113	0.6236 ± 0.033	0.7160 ± 0.041	12.90 ± 2.001	1.14 ± 0.056
F7	28.79 ± 1.670	0.6367 ± 0.019	0.7434 ± 0.057	14.35 ± 0.987	1.16 ± 0.078
F8	29.87 ± 0.888	0.6321 ± 0.044	0.7323 ± 0.034	13.68 ± 0.789	1.15 ± 0.033
F9	30.18 ± 0.716	0.6298 ± 0.051	0.7269 ± 0.056	13.35 ± 1.003	1.15 ± 0.067

Table 3: IPQC Test Results of Film Coated Tablets (n=20)

Batch No.	Average weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	250 ± 0.76	3.625 ± 0.3	9.68 ± 0.2	4.5 ± 0.37	0.011 ± 0.59	80.9 ± 1.08
F2	250 ± 1.22	3.650 ± 0.3	9.68 ± 0.2	7.0 ± 0.70	0.015 ± 0.94	83.5 ± 0.39
F3	250 ± 1.02	3.55 ± 0.3	9.68 ± 0.2	5.5 ± 0.11	0.027 ± 0.47	89.7 ± 0.22
F4	250 ± 0.64	3.55 ± 0.3	9.68 ± 0.2	5.5 ± 0.65	0.024 ± 0.22	97.2 ± 0.65
F5	250 ± 0.84	3.65 ± 0.3	9.68 ± 0.2	4.5 ± 0.72	0.010 ± 0.13	95.9 ± 1.99
F6	250 ± 0.44	3.75 ± 0.3	9.68 ± 0.2	6.5 ± 0.23	0.011 ± 0.98	102.0 ± 0.97
F7	250 ± 0.99	3.75 ± 0.3	9.68 ± 0.2	6.5 ± 0.34	0.044 ± 0.57	101.4 ± 1.12
F8	250 ± 1.44	3.65 ± 0.3	9.68 ± 0.2	6.0 ± 0.83	0.090 ± 1.24	99.8 ± 0.74
F9	250 ± 1.12	3.725 ± 0.3	9.68 ± 0.2	7.0 ± 0.56	0.120 ± 1.33	98.76 ± 1.56

Table 4: Comparison of % cumulative drug release of film coated tablets of different batches (n=6)

Media	F1	F2	F3	F4	F5	F6	F7	F8	F9
Buffer pH 7.2 (1 hour)	20.0±1.02	11.7±0.88	32.0±1.23	22.0±2.01	02.15±0.87	15.0 ± 0.98	12.8 ± 1.45	13.0 ± 0.56	11.1 ± 0.74
Buffer pH 7.2 (3 hours)	38.7±0.99	26.7±0.97	89.6±0.56	49.0±1.67	23.45±0.69	33.8 ± 0.76	48.8 ± 1.78	45.2 ± 1.13	44.5 ± 0.89
Buffer pH 7.2 (10 hours)	80.0±0.73	79.4 ± .77	-	96.4±1.89	85.6 ± 1.11	101.8±0.72	98.9 ± 0.96	99.2 ± 1.78	97.6 ± 1.57

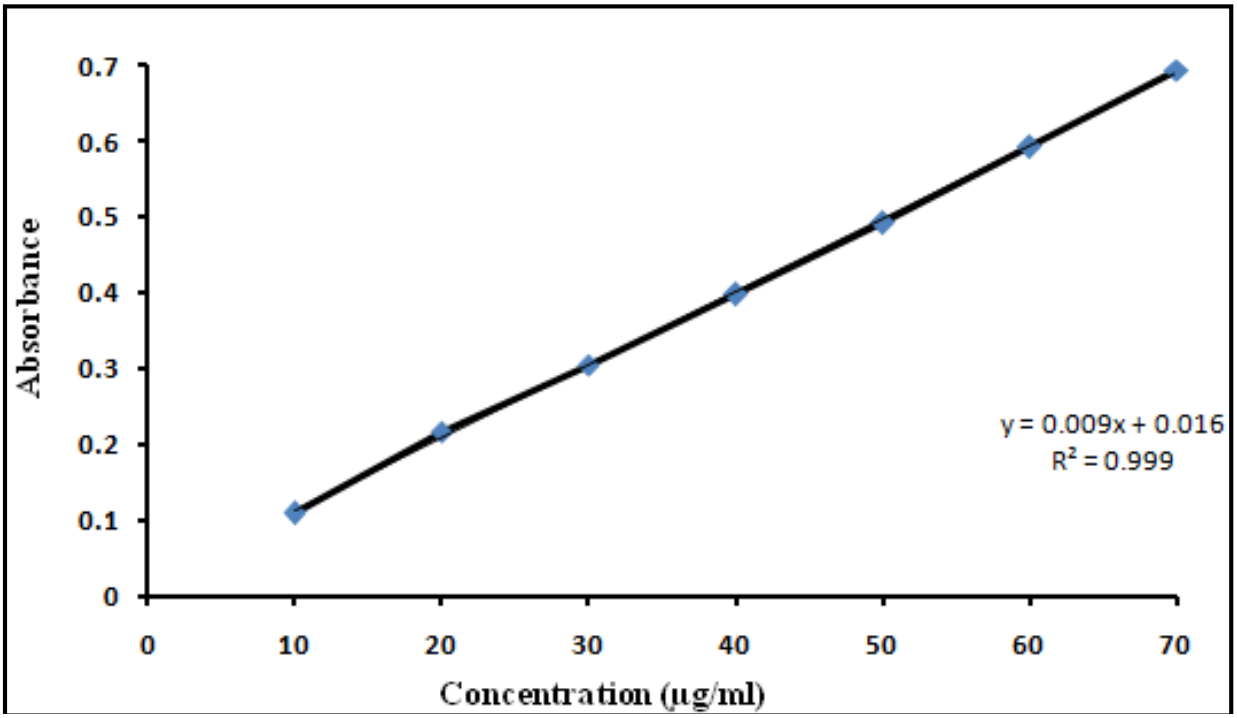

Fig 1: Calibration curve of nitrofurantoin

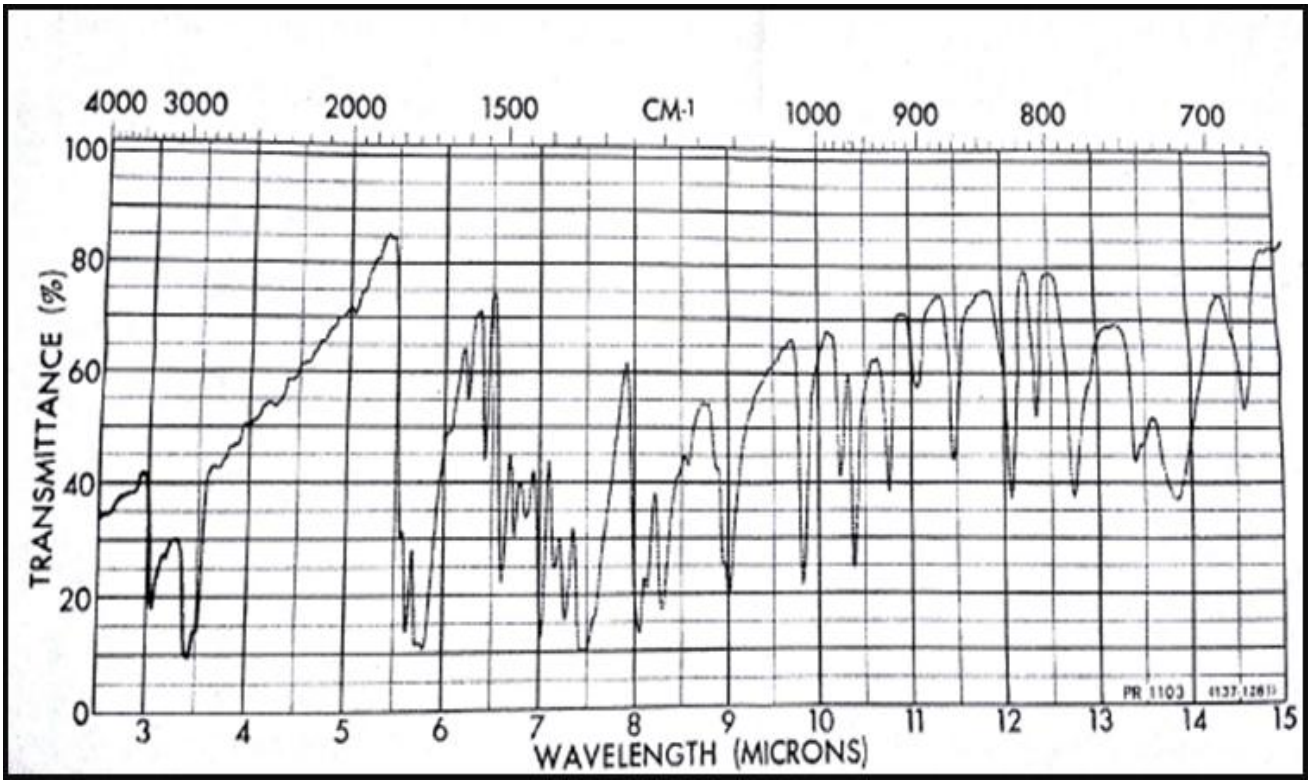

Fig 2: IR spectrum of nitrofurantoin

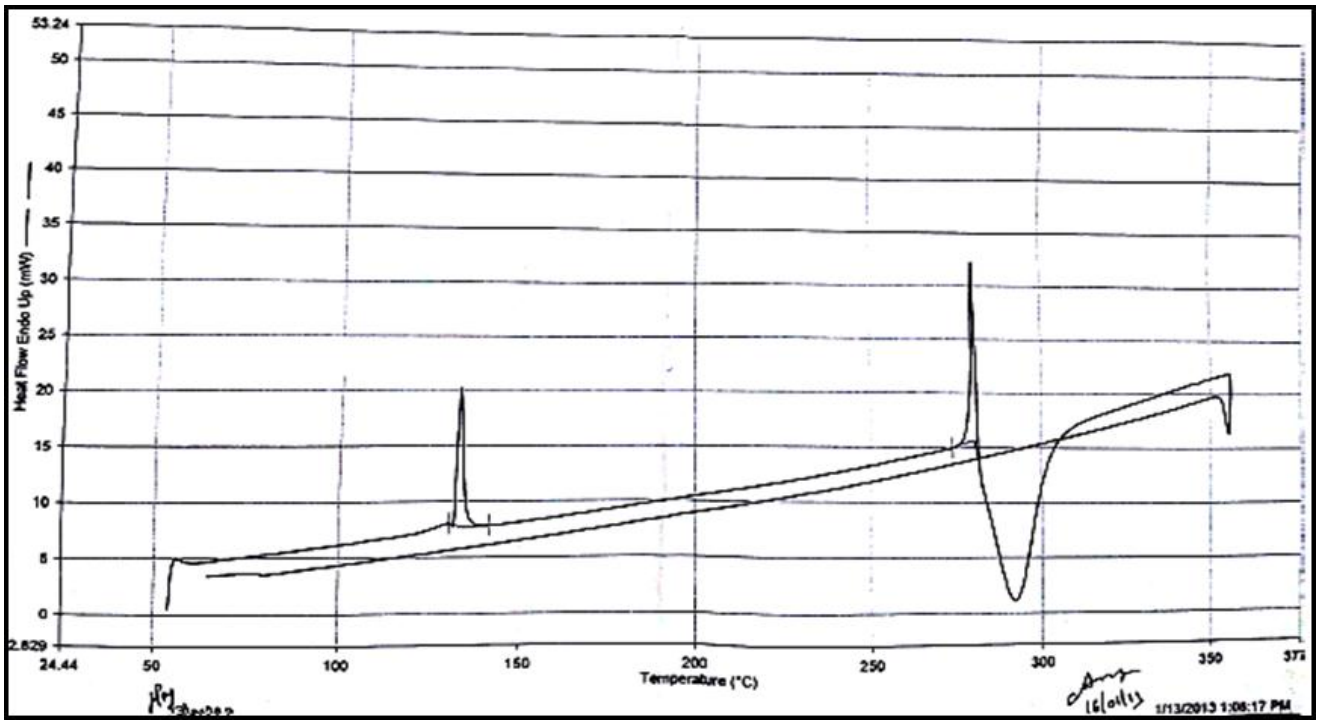

Fig 3: DSC of nitrofurantoin

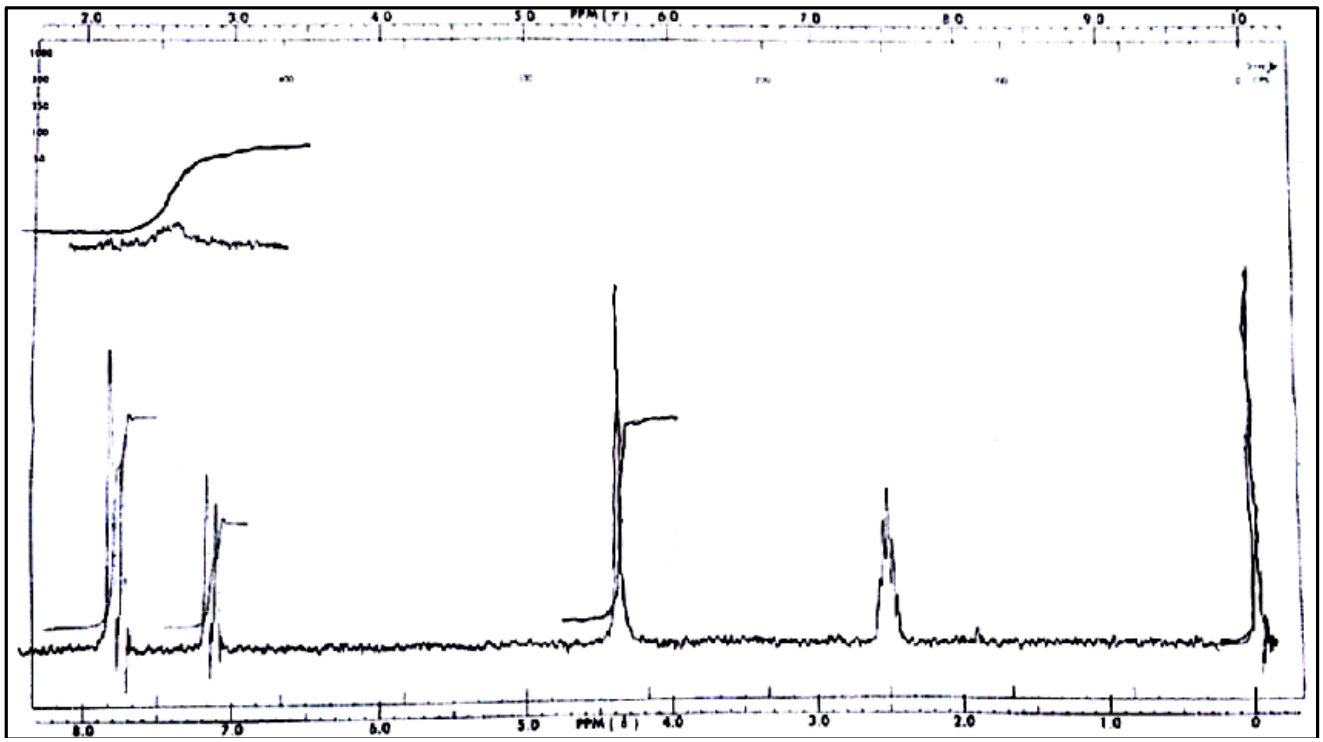

Fig 4: NMR spectrum of nitrofurantoin

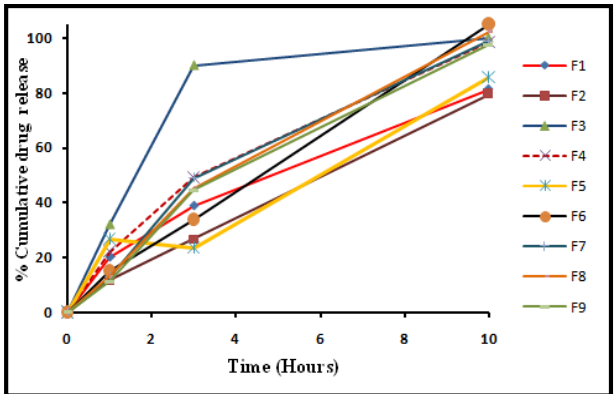

Fig 5: % Cumulative Drug Release of Film-Coated SR Tablets of nitrofurantoin of Different Batches (Zero-order plot)

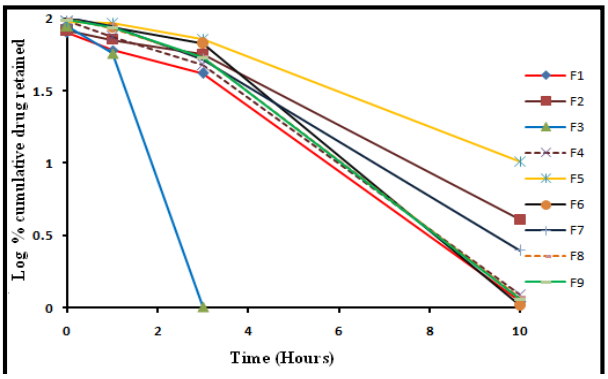

Fig 6: First order plot of *in vitro* drug release study of different batches of film-coated SR tablets of nitrofurantoin

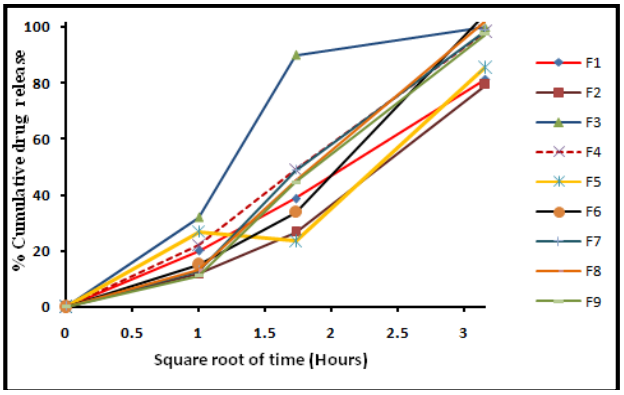

Fig 7: Higuchi plot of *in vitro* drug release study of different batches of film-coated SR tablets of nitrofurantoin

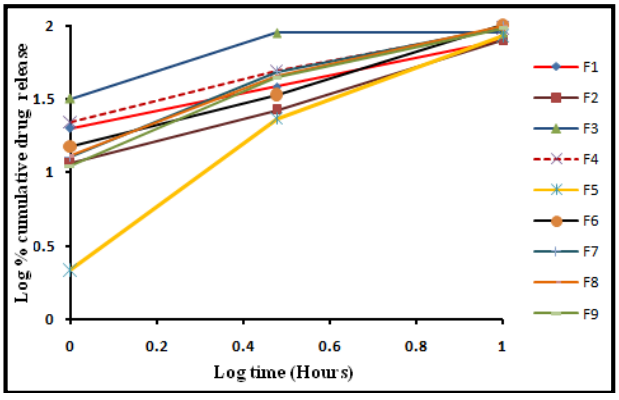

Fig 8: Korsemeyer-Peppas plot of *in vitro* drug release study of different batches of film-coated SR tablets of nitrofurantoin

Conclusion

The present study was undertaken with the aim to formulate and evaluate nitrofurantoin sustained release tablets. The study reveals that formulation F6 is an ideal or optimized formulation for sustained release tablets, as it fulfills all the requirements for sustained release tablets. The reproducibility and accuracy of formulation was required further in-vivo studies and continuation of stability studies is also recommended.

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